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# Evolution of the Sweetness Receptor in Primates. I. Why Does Alitame Taste Sweet in all Prosimians and Simians, and Aspartame only in Old World Simians?

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## Abstract

In the order Primates the responses to sucrose, alitame and aspartame were ascertained. All primates tested to date like sucrose and prefer this sweet substance to tap water. The artificial dipeptide aspartame was found to be not sweet in Prosimii and Platyrrhini (New World monkeys). Only the Cercopithecoidea (Old World monkeys) and Hominoidea (apes and humans) show the same response to aspartame and to sucrose. In contrast, all primates tested so far prefer alitame, another artificial dipeptide sweetener, which is structurally closely related to aspartame. This phylogenetic difference is consistent with the existence in catarrhine primates of a sweetness receptor containing two differently located hydrophobic recognition sites, one for the hydrophobic binding site of alitame, the other for the hydrophobic binding site of aspartame. On the basis of these results, it is suggested that the alitame-related hydrophobic recognition site, which is found in the sweetness receptor of all primates, could be a requisite for the interaction of the receptor with sucrose, while the aspartame-related hydrophobic recognition site, which is found exclusively in the sweetness receptor of Old World simians, could have been a crucial factor in the improvement in detection or selection of sucrose in foods, so favouring the mental development of these simians and maybe the emergence of humans. Chem. Senses 20: 573–584, 1995.

## Introduction

Aspartame (L-aspartyl-L-phenylalanine methyl ester), an artificial dipeptide sweetener (Figure 1) which is, on a weight basis, about 180 times more potent than sucrose in man (Schlatter, 1966; Mazur *et al.*, 1969; Mazur, 1984), has the feature of being sweet only in Catarrhini (Old World simians), but not in Platyrrhini (New World simians) or Prosimii (prosimians) (Glaser *et al.*, 1992; Glaser, 1993). Like aspartame, thaumatin, an intensely sweet protein in man consisting of a single polypeptide chain of 207 amino acids (Iyengar *et al.*, 1979) which is, on a weight basis, around 1600 times sweeter than sucrose (van der Wel and Loeve, 1972), is sweet only in Catarrhini (Glaser *et al.*,

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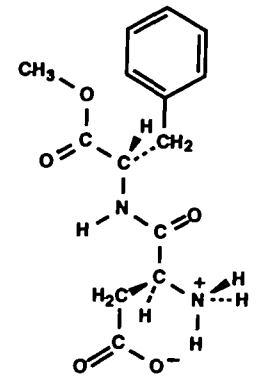

**Figure 1** Aspartame, an artificial dipeptide sweetener

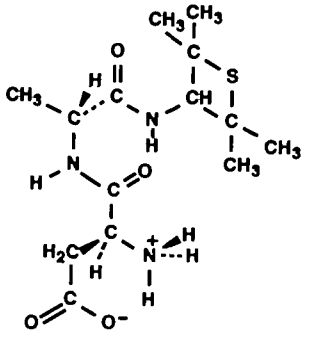

**Figure 2** Alitame, an artificial dipeptide sweetener

1978; Glaser, 1994), which evokes a common mechanism of action for aspartame and thaumatin at the sweetness receptor level. Currently, nothing is known about the exact molecular reason and the real significance of this very surprising mutation which appeared in the Old World simian stock and persisted through time, to the present day in all the catarrhine species, including man. While attempting to understand the molecular meaning of this dichotomy within primates, we observed that alitame (L-aspartyl-D-alanine 2,2,4,4-tetramethylthietanylamide), another artificial dipeptide sweetener (Figure 2) with a structure closely related to aspartame and with a sweetness potency of about 2000 times that of sucrose in man (Brennan and Hendrick, 1981; Glowaki *et al.*, 1991) is, unlike aspartame, unexpectedly sweet to all primates tested, including prosimians and New World simians. This is the subject of the present study.

## Materials and methods

### Sweeteners

Alitame (ALT) was prepared by the method described by Brennan and Hendrick (1981). Aspartame (APM) and sucrose were obtained from a commercial source.

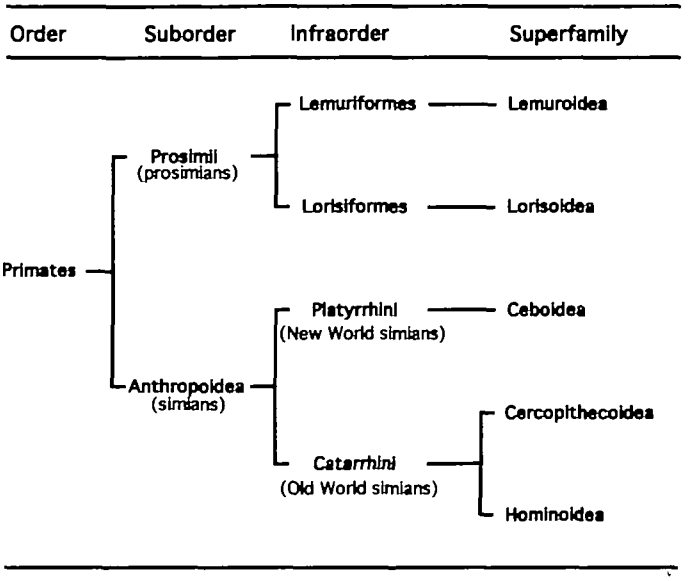


**Figure 3** Simplified classification of the primates used in the present study.

### Animals

The prosimians used in this study were chosen, from the superfamilies Lemuroidea (Madagascar) and Lorisoidea (Asia), the New World simians (from South and Central America) from the superfamily Ceboidea, and the Old World simians from the superfamilies Cercopithecoidea (Africa, Asia) and Hominoidea (see Figure 3). Sweeteners were tested in 42 species or subspecies of primates.

Among the prosimians, in the superfamily Lemuroidea, we used: *Lemur catta* (ring-tailed lemur), *Eulemur mongoz* (mongoose lemur), *Eulemur macaco macaco* (black lemur), *Eulemur macaco flavifrons* (Sclater's lemur), *Eulemur fulvus albifrons* (white-fronted brown lemur), *Eulemur coronatus* (crowned lemur), *Eulemur rubriventer* (red-bellied lemur), *Varecia variegata variegata* (black-ruffed lemur), *Varecia variegata rubra* (red-ruffed lemur) and *Hapalemur griseus occidentalis* (western gentle lemur); in the superfamily Lorisoidea, we used: *Nycticebus pygmaeus* (pygmy slow loris).

Among the New World simians, in the superfamily Ceboidea, we used: *Cebuella pygmaea* (pygmy marmoset), *Callithrix jacchus jacchus* (common marmoset), *Callithrix jacchus geoffroyi* (white-fronted marmoset), *Saguinus labiatus labiatus* (white-lipped tamarin), *Saguinus imperator subgrisescens* (emperor tamarin), *Leontopithecus rosalia rosalia* (golden lion tamarin), *Leontopithecus rosalia chrysomelas* (golden-headed tamarin). *Callimico goeldii* (Goeldi's monkey), *Aotus trivirgatus* (owl or night monkey), *Pithecia*

*pithecia* (paleheaded saki), *Cebus appella xanthosternos* (yellow-breasted capuchin monkey), *Saimiri sciureus* (common squirrel monkey) and *Ateles geoffroyi* (black-handed spider monkey).

Among the Old World simians, in the superfamily Cercopithecoidea (Old World monkeys), we used: *Macaca arctoides* (stump-tailed macaque), *Macaca nigra* (Celebes black macaque), *Papio anubis* (olive baboon), *Papio papio* (Guinea baboon), *Papio hamadryas* (hamadryas baboon), *Cercopithecus diana roloway* (Roloway guenon), *Cercopithecus preussi* (Preuss's guenon), *Allenopithecus nigroviridis* (Allen's swamp monkey), *Erythrocebus patas patas* (patas monkey) and *Presbytis entellus* (Hanuman langur); in the superfamily Hominoidea (apes and humans), we used: *Hylobates pileatus* (pileated gibbon), *Hylobates syndactylus* (siamang), *Pongo pygmaeus pygmaeus* (Borneo orang-utan), *Pongo pygmaeus abelii* (Sumatra orang-utan), *Gorilla gorilla gorilla* (western lowland gorilla), *Pan paniscus* (pygmy chimpanzee), *Pan troglodytes troglodytes* (common chimpanzee) and *Homo sapiens sapiens* (human).

The systematic relationships within the order of Primates are still under discussion even at the family level. For this reason, in the present study we used only a simplified classification at the superfamily level. For additional information regarding the taxonomic status of the species mentioned in this paper see, for example, Napier and Napier (1972), Corbet and Hill (1980), Mittermeier *et al.* (1992), Rylands *et al.* (1993), Snowdon (1993), Groves (1993) and Geissmann (1994).

## Methods

Desiring to use a large variety of animal species to try to understand the evolution of the sweetness receptor in primates, and on account of the rarity of certain species used (these being, furthermore, often endangered or protected), it was evidently impossible for us to employ conventional electrophysiological recordings from the chorda tympani nerve or conditioned taste aversion tests. In accordance with our own ethic, and the guiding principles in the care and use of animals, we only used in this study two appropriated, but complementary behavioural tests, namely the two-bottle preference test combined with observation of the taste-induced hedonic modifications of facial expression, where these exist.

Detailed descriptions of the methods used for aspartame can be found in a previous paper of Glaser *et al.* (1992).

The two-bottle preference test was employed to judge preference (+) to a solution of alitame (at a concentration of 100 mg/l) or otherwise no response or avoidance (−) against tap water. The smaller sized animals were offered the choice of two bottles attached to the cage. The medium-sized animals were provided with two larger drinking bowls, which were placed inside the cages. The Hylobatidae and Pongidae were tested with the aid of their usual drinking mugs. So all animals were able to choose between the alitame solution and tap water. We randomly changed the side of the alitame solution offered. The tests starting early in the morning, the animals had been deprived of fluid intake since the evening before. Each animal was therefore in a thirsty condition. Finally, the intake of alitame solution versus water was measured and compared.

Taste-induced facial expressions clearly show that gustatory stimuli such as sucrose, aspartame or alitame trigger behavioural responses, both in non-human primates and in man which truly mirror 'hedonic aspects' of gustatory experience (Steiner and Glaser, 1984, 1995). These observations were a help in judging primates' behaviour when tasting a sweet solution (facial expressions such as sampling-sipping, lapping or eager drinking, quick swallow, mouth open, lips apart, sucking-smacking, head orientated towards stimulus), that was clearly differentiable from those patterns of behaviour triggered by other qualities or simply by tap water (e.g. mouth corners down, spitting, head turn/head shake, gaping, head withdrawal from stimulus). Nearly all primates tested have shown these patterns and this behaviour is not species-specific.

These behavioural studies were made in the Zoological Garden of Frankfurt (14 species), in the Parc Zoologique et Botanique de Mulhouse (13 species), in the primate facilities of Ciba-Geigy and Hoffmann-LaRoche, Basel (four species), in the Zoological Garden of Zürich (15 species) and in the Anthropological Institute of the University of Zürich-Irchel (four species). It was possible to duplicate experiments at two different facilities with nine species (*Varecia variegata rubra, Cebuella pygmaea, Callithrix jacchus geoffroyi, Leontopithecus rosalia rosalia, Callimico goeldii, Pongo pygmaeus pygmaeus, Pongo pygmaeus abelii, Gorilla gorilla gorilla, Pan troglodytes troglodytes*), but always we obtained the same behavioural reactions.

Whatever the location—the Zoological Gardens or the other facilities—the fixed behaviour patterns to the substance were mainly observed. In shy and nocturnal animals (*Hapalemur griseus occidentalis, Nycticebus pygmaeus, Aotus trivirgatus*) this was not possible and only the two-bottle preference test was employed.

**Table 1** Compared taste responses of primates to sucrose, alitame and aspartame

| Species | Sucrose | Alitame | Aspartame |
|---|---|---|---|
| Prosimii: | | | |
| Lemuroidea | | | |
| *Lemur catta* | + | + | − |
| *Eulemur mongoz* | + | + | − |
| *Eulemur macaco macaco* | + | + | − |
| *Eulemur macaco flavifrons* | + | + | − |
| *Eulemur fulvus albifrons* | + | + | − |
| *Eulemur coronatus* | + | + | − |
| *Eulemur rubriventer* | + | + | − |
| *Varecia variegata variegata* | + | + | − |
| *Varecia variegata rubra* | + | + | − |
| *Hapalemur griseus occidentalis* | + | + | − |
| Lorisoidea | | | |
| *Nycticebus pygmaeus* | + | + | − |
| Anthropoidea: | | | |
| Ceboidea | | | |
| *Cebuella pygmaea* | + | + | − |
| *Callithrix jacchus jacchus* | + | + | − |
| *Callithrix jacchus geoffroyi* | + | + | − |
| *Saguinus labiatus labiatus* | + | + | − |
| *Saguinus imperator subgrisescens* | + | + | − |
| *Leontopithecus rosalia rosalia* | + | + | − |
| *Leontopithecus rosalia chrysomelas* | + | + | − |
| *Callimico goeldii* | + | + | − |
| *Aotus trivirgatus* | + | + | − |
| *Pithecia pithecia* | + | + | − |
| *Cebus apella xanthosternos* | + | + | − |
| *Saimiri sciureus* | + | + | − |
| *Ateles geoffroyi* | + | + | − |
| Cercopithecoidea | | | |
| *Macaca arctoides* | + | + | + |
| *Macaca nigra* | + | + | + |
| *Papio anubis* | + | + | + |
| *Papio papio* | + | + | + |
| *Papio hamadryas* | + | + | + |
| *Cercopithecus diana roloway* | + | + | + |
| *Cercopithecus preussi* | + | + | + |
| *Allenopithecus nigroviridis* | + | + | + |
| *Erythrocebus patas patas* | + | + | + |
| *Presbytis entellus* | + | + | + |
| Hominoidea | | | |
| *Hylobates pileatus* | + | + | + |
| *Hylobates syndactylus* | + | + | + |
| *Pongo pygmaeus pygmaeus* | + | + | + |
| *Pongo pygmaeus abelii* | + | + | + |
| *Gorilla gorilla gorilla* | + | + | + |
| *Pan paniscus* | + | + | + |
| *Pan troglodytes troglodytes* | + | + | + |
| *Homo sapiens sapiens* | + | + | + |

## Results

The results obtained are given in Table 1.

These results clearly indicate that alitame, exactly like sucrose, is preferred in the 42 primates tested, including prosimians, and New World and Old World simians, while aspartame is preferred only by Old World simians.

## Discussion

The preceding results lead us to infer that the primate sweetness receptor was able to interact with alitame before the date of divergence of prosimians and simians, since all modern prosimians and simians tested respond positively to alitame.

The mutation which has enabled the primate sweetness receptor to interact with aspartame must be much more recent in comparison to the alitame feature, since it is detected only in Old World simians, but not in prosimians and New World simians. The lineage of 'responding to aspartame' descends from the radiation in the Oligocene and if the generic classification of the Fayum Anthropoidea by Simons and Rasmussen (1991) is reliable, the age of the earliest known well-dated Catarrhini is approximately 35.7 million years (Kappelman, 1992).

As discussed in an earlier contribution concerning thaumatin (Glaser, 1994), *Amphipithecus* and *Pondaungia*, from the late Eocene (about 40–44 MYA), discovered in Burma, have long been considered as early anthropoids, but a reappraisal of these species demonstrates that they are not anthropoids (Ciochon and Holroyd, 1994). *Algeripithecus*, another new discovery from an Algerian locality (Godinot and Mahboubi, 1992), with an age of approximately 46–50 million years, is assumed to be closer to the parapithecids, and therefore could not be classed as a catarrhine (Simons *et al.*, 1994).

The first finding of a platyrrhine fossil from South America is of Oligocene age (Holroyd and Maas, 1994). If we assume that the splitting of the Anthropoidea into platyrrhines and catarrhines occurred some several million years before, this aspartame discriminating feature may be about 38–40 MYA. An earlier date of splitting of these two groups mentioned above with 55 MYA (see Martin, 1990) is computer-calculated and not confirmed by fossils. More recent details can be found in *Anthropoid Origins* (Fleagle and Kay, 1994). Finally, the taste results with aspartame and other taste-physiological data we have so far do not confirm the hypothesis of Ford (1994) that the 'Anthropoidea do form a monophyletic clade'.

What molecular features can be at the origin of this disparity in the primate taste responses between alitame and aspartame?

The relationships between the structure and taste of sweeteners in man have been studied by many authors. In particular, Shallenberger and Acree (1967), in a pioneering work, postulated that the sweetness of a compound is the consequence of the presence in the molecule of two groups: a hydrogen-bond donor group (denoted as AH) and a hydrogen-bond acceptor group (denoted as B), separated by about 0.3 nm; in this case, the AH,B unit is able to bind through intermolecular hydrogen bonds to a hypothetical complementary AH,B unit of the sweetness receptor permitting the molecule to be perceived as sweet. In the sweet dipeptides, the ammonium group ($NH_3^+$) is assumed to be the AH binding site and the carboxylate group ($COO^-$) the B binding site of the Shallenberger and Acree theory (Lelj *et al.*, 1976; Temussi *et al.*, 1978; van der Heijden *et al.*, 1978).

To explain the differences in sweetness potency between certain sweet molecules, Kier (1972) speculated that potent sweeteners must contain a third binding site with the capacity to interact with the receptor via 'dispersion forces', now regarded as 'hydrophobic interactions'. This putative third site was successively designated as X by Kier (1972), $\gamma$ by Shallenberger and Lindley (1977), $\delta$ by van der Heijden *et al.* (1978), and G by Tinti and Nofre (1991), as a result of strong differences in the assignment of the involved groups or atoms in related or *a fortiori* in unrelated sweeteners. The phenyl group ($C_6H_5$) in aspartame (Lelj *et al.*, 1976; Temussi *et al.*, 1978; van der Heijden *et al.*, 1978) and the 2,2,4,4-tetramethylthietanyl group ($C_7H_{13}S$) in alitame (Feinstein *et al.*, 1991) were accordingly proposed as the hydrophobic binding sites of these two sweeteners.

In the dipeptide sweeteners, other groups are probably involved in the interaction with the receptor. This is the case for the peptide bond (CONH) linking the aspartyl residue to the second amino acid, particularly its NH part which has been considered as a putative binding site (XH binding site; Tinti and Nofre, 1991). For example, in aspartame, an *N*-methylation of the NH group (CONMe), a 'retro-inverso' peptide modification (NHCO) or the replacement of the peptide bond by an ester bond (COO) have the effect of suppressing the sweetness (MacDonald *et al.*, 1980). As the peptide bond is a common part of aspartame and alitame, obviously it cannot be involved in the dichotomic response observed with aspartame in the primates. Of course, the same is true for the $NH_3^+$ group (the AH binding site) and

the $COO^-$ group (the B binding site) which are also common to both molecules.

Another group possibly involved in the interaction of aspartame with the sweetness receptor is the methyl carboxylate group ($COOCH_3$) denoted as an $E_1$ binding site following the terminology proposed by Tinti and Nofre (1991) for the binding sites of sweeteners. In fact, the interaction of this group is not essential to the sweetness of this dipeptide since the replacement of the $COOCH_3$ group of aspartame (Figure 4a) by a $CH_3$ group leads to a compound (Figure 4b) which is still about 50 times sweeter than sucrose in man (Mazur *et al.*, 1970, 1973). Consequently, in aspartame, the $COOCH_3$ group must be considered as only a sweetness amplifying group, increasing the sweetness potency by a factor of about 3.5 in comparison with a $CH_3$ group.

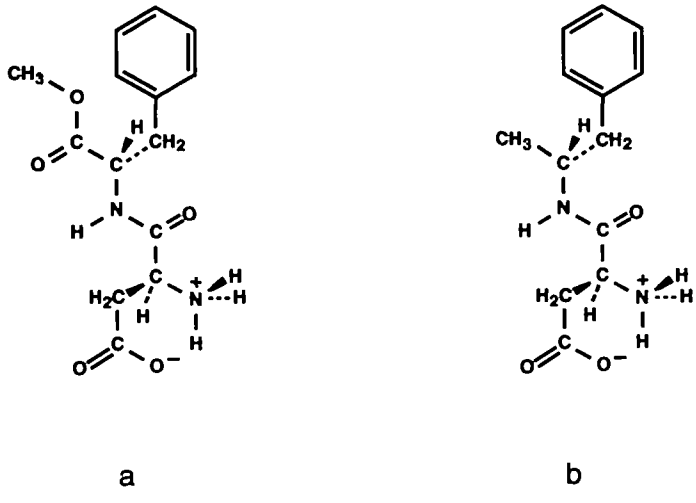


**Figure 4** The role of $COOCH_3$ as a sweetness intensifying group: (a) aspartame (×180 sucrose); (b) *N*-α-L-aspartyl-(*R*)-α-methylphenethylamine (×50).

Now if we consider the hydrophobic moieties of aspartame and alitame, it is known that the replacement in aspartame (Figure 5a) of the phenyl group by a hydrogen atom leads to a compound (Figure 5b) which is not sweet at all in man (Mazur *et al.*, 1969). In the same way, the replacement of the 2,2,4,4-tetramethylthietanyl group of alitame (Figure 5c) by a hydrogen atom leads to an unsweet molecule (Figure 5d) (Sukehiro *et al.*, 1977).

In consequence, the fact that alitame is tasted sweet by all primates, but aspartame only by the Old World simians can only be explained by a fundamental difference in the interaction of their respective hydrophobic binding sites (G sites) with the sweet-dipeptide receptor. The evidence is for the presence in the sweet-dipeptide receptor of prosimians and New World simians of one site of hydrophobic recognition which is able to interact with the hydrophobic binding site of alitame ($G_{ALT}$ binding site) and for the co-existence in the sweet-dipeptide receptor of Old World simians of two independent sites of hydrophobic recognition, one being able to detect the hydrophobic binding site of alitame ($G_{ALT}$ binding site) and the other the hydrophobic binding site of aspartame ($G_{APM}$ binding site).

Moreover, Nofre and Tinti (1992) have recently shown, in an extensive programme of research into new potent artificial sweeteners, that the attachment of a second hydrophobic group to the aspartame molecule leads to new, very

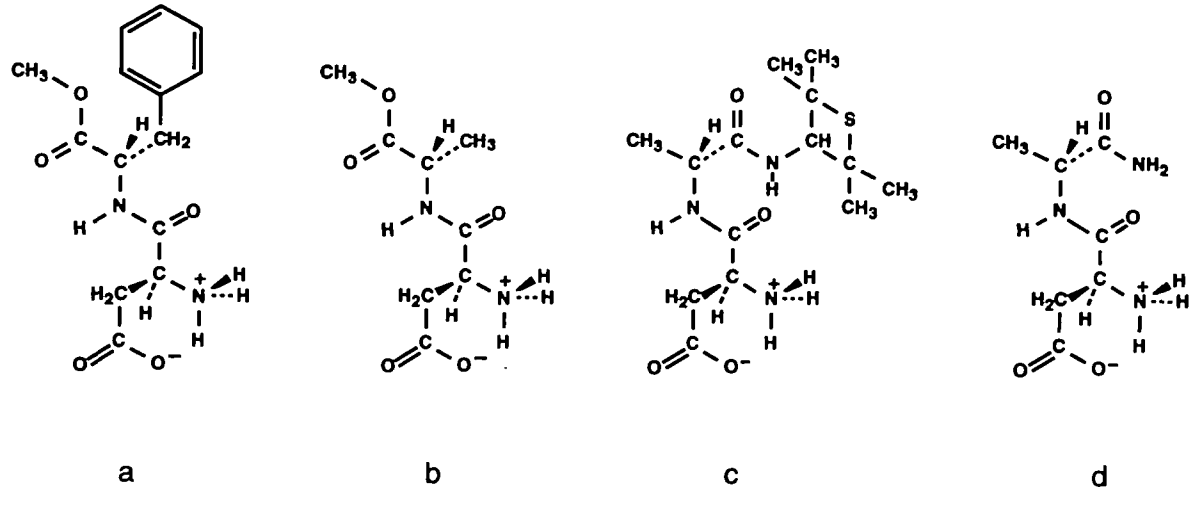


**Figure 5** Contribution of the hydrophobic part of aspartame and alitame to sweetness: (a) aspartame (×180 sucrose); (b) L-aspartyl-L-alanine methyl ester (not sweet); (c) alitame (×2000); (d) L-aspartyl-D-alaninamide (not sweet).

powerful sweeteners, such as *N*-(3,3-dimethylbutyl)-L-α-aspartyl-L-phenylalanine methyl ester (Figure 6) which has a sweetness potency of about 10 000 times that of sucrose in man and more than 50 times that of aspartame. This finding is an additional proof of the existence of two separate hydrophobic recognition sites in the human sweet-dipeptide receptor capable of recognizing simultaneously the two distinct hydrophobic groups of these recently discovered hybrid molecules. The existence of these hybrid molecules also enables us to discard the highly improbable possibility of two distinctive types of sweet-dipeptide receptors in man (and therefore in the apes and Old World monkeys), one for alitame, the other for aspartame.

What are the relative locations of the hydrophobic groups of alitame and aspartame when they interact with the sweetness receptor to elicit a sweet taste?

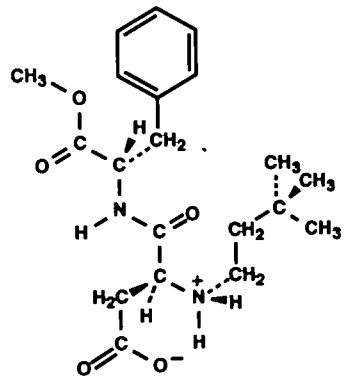

**Figure 6** *N*-(3,3-dimethylbutyl)-L-α-aspartyl-L-phenylalanine methyl ester.

According to Feinstein *et al.* (1991), the preferred conformation of alitame can be described as possessing an L shape, with the $COO^-$ and $NH_3^+$ containing aspartyl moiety as the stem of the L and the hydrophobic tetramethylthietanyl moiety as the base of the L, nearly perpendicular to the aspartyl residue backbone (Figure 7a). For aspartame, the current opinion is that aspartame in solution can exist under two quasi-isoenergetic conformations in dynamic equilibrium (Castiglione-Morelli *et al.*, 1990; Taylor *et al.*, 1991), one in an extended conformation with the phenyl ring approximately parallel to the zwitterionic ring of the aspartyl residue and in an almost direct line with the aspartyl residue axis (Figure 7b), the other in an L-shaped conformation rather similar to the overall conformation of alitame, with the phenyl group roughly perpendicular to the aspartyl residue (Figure 7c). The interconversion of the L-shaped conformation (which appears to be the most populated conformation in solution) to the extended conformation requires less than 1 kcal/mol, a modest value that can be easily compensated for by the interaction with receptor (Castiglione-Morelli *et al.*, 1990).

Most of the proposed theoretical models of the aspartame receptor support the idea of an interaction of aspartame with the sweetness receptor in its L-shaped conformation (van der Heijden *et al.*, 1978, 1979, 1985; Goodman *et al.*, 1987; Benedetti *et al.*, 1990; Douglas and Goodman, 1991; DuBois *et al.*, 1993) and of an interaction of the hydrophobic binding site of both alitame and aspartame with a common hydrophobic recognition site of the receptor (Douglas and Goodman, 1991; Feinstein *et al.* 1991).

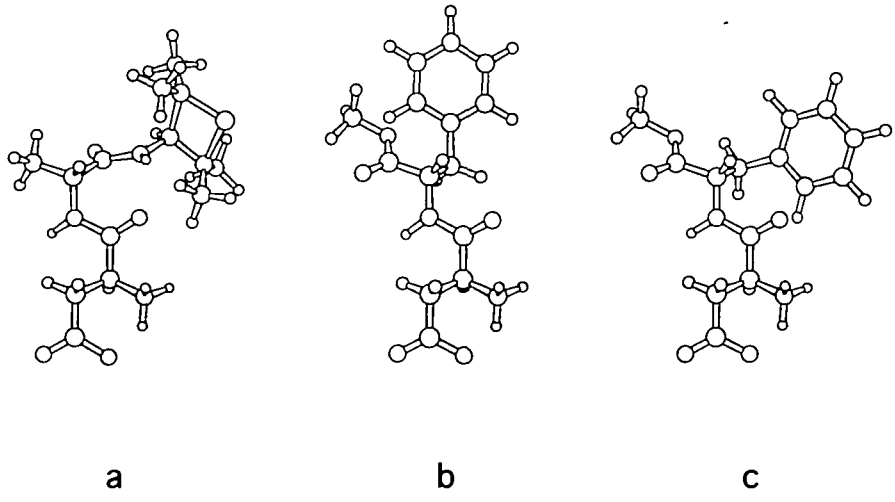


**Figure 7** (a) Preferred conformation of alitame in solution (Feinstein *et al.*, 1991), (b) and (c) the two preferred and quasi-isoenergetic conformations of aspartame in solution (Castiglione-Morelli *et al.*, 1990).

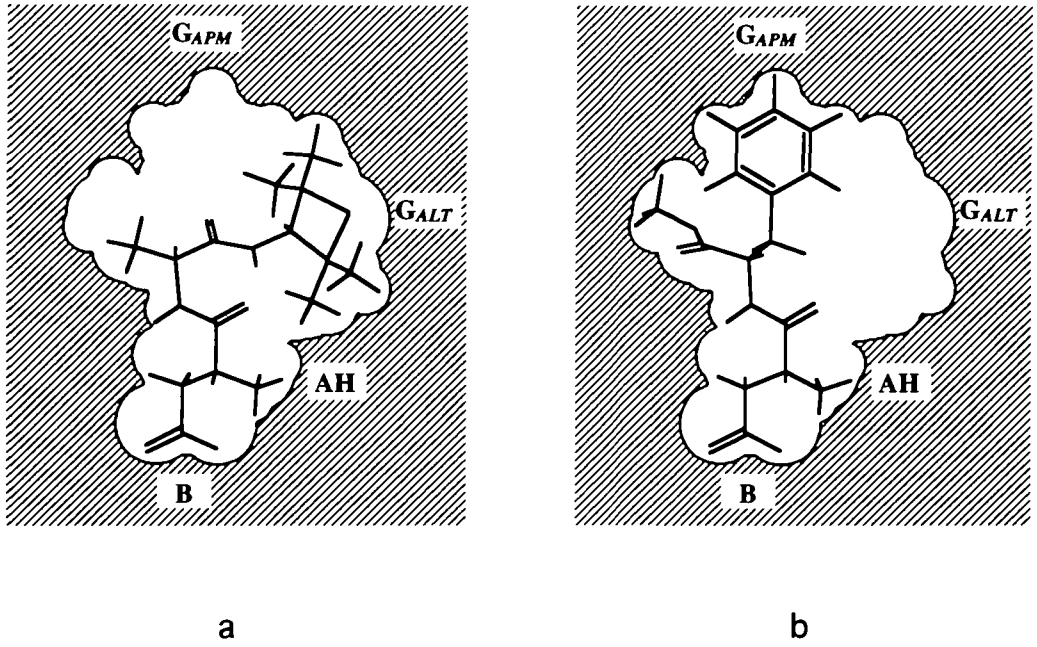


**Figure 8** Model of the Old World simian (including man) sweetness receptor able to interact indifferently with (a) alitame or (b) aspartame and elicit a sweet response, the contour of this idealized model was drawn from a superimposition of space-filling models of alitame in its L-shaped conformation and aspartame in its extended conformation

Contrary to the preceding assertions, since the present work substantiates the existence of two distinct hydrophobic recognition sites within the sweetness receptor of humans, apes and Old World monkeys, it follows that alitame must interact with the sweetness receptor in an L-shaped conformation (Figure 7a) according to the Goodman model (Douglas and Goodman, 1991; Feinstein *et al.*, 1991) and aspartame must interact with the sweetness receptor in its extended conformation (Figure 7b) in agreement with the Temussi proposal (Lelj *et al.*, 1976; Temussi *et al.*, 1978, 1991; Castiglione-Morelli *et al.*, 1990).

On the basis of our present knowledge, we can therefore imagine the sweetness receptor of the Old World simians (catarrhine primates) as a rather complex cavity inside the receptor protein (see Figure 8 for an idealized representation) made up of a series of several interconnected pockets (the receptor recognition sites) two of which (here denoted as the $G_{ALT}$ and $G_{APM}$ pockets) are able to interact either with the hydrophobic site of alitame (Figure 8a) or with the hydrophobic site of aspartame (Figure 8b).

The sweetness receptor of both prosimians and New World simians (non-catarrhine primates) should be structurally close to the Old World simian receptor except for the $G_{APM}$ pocket which could be either non-functional (due to the lack of appropriate interacting groups on the receptor protein) (Figure 9a) or even absent (through a steric occlusion) (Figure 9b). It must be noted that the present data do not enable us to know if the $E_1$ recognition site of the non-catarrhine primate receptor is different from that of the catarrhine primate receptor. Since aspartame also appears to be non-sweet to rodents (see Jakinovich and Sugarman, 1989) such as the hamster (Nowlis *et al.*, 1980), the gerbil (Jakinovich, 1981) or the rat (Nowlis *et al.*, 1980; Hellekant and Walters, 1992), we can logically suppose that rodents should have a sweet-taste receptor closely related to the one of the non-catarrhine primates.

Since thaumatin, exactly like aspartame, is sweet to Catarrhini, but not sweet to Prosimii and Platyrrhini (Glaser *et al.*, 1978; Glaser, 1994), one can also logically assume that this sweet protein must interact with the $G_{APM}$ pocket of the receptor, through a hydrophobic side chain of a still unidentified amino-acid residue of this sweet-tasting protein. Moreover, as thaumatin elicits no response in any of the non-primate mammals tested, such as guinea-pigs, rats (Brouwer *et al.*, 1973), hamsters, rabbits, dogs, pigs (Hellekant, 1976), calves (Hård af Segerstad and Hellekant, 1989a, b), sheep, horses (Glaser, 1994), tree shrew (*Tupaia belangeri*) and the pygmy hedgehog tenrec (*Echinops telfairi*) (Glaser *et al.*, 1978), it can be inferred that the absence of a $G_{APM}$ pocket is a permanent feature of the sweetness receptors of all placental mammals, except for the Catarrhini.

Now it remains to be seen why, more than 35 million

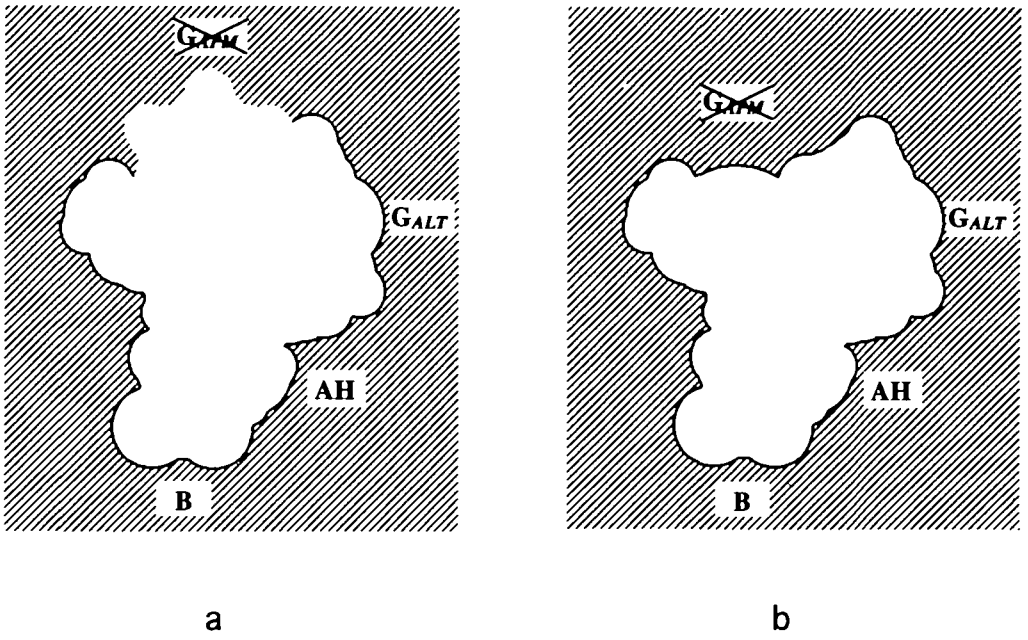


**Figure 9** Two possible models of the prosimian and New World simian sweetness receptor both able to interact with alitame and elicit a sweet response: (a) model in which aspartame is sterically able to fit into the receptor, but is unable to elicit a sweet response owing to a non-functional $G_{APM}$ pocket; (b) model in which aspartame is unable to fit into the receptor and to elicit a sweet response owing to a sterically occluded $G_{APM}$ pocket.

years ago, a mutation appeared in the sweetness receptor of the Old World simians making them able to taste aspartame, an artificial sweetener, and why this mutation was invariably preserved until now in all Catarrhini, including man. It also remains to be seen what the significance is of this ability of the sweet-taste receptor of all primates studied, from the most primitive to apes and humans, to be stimulated by alitame, another artificial sweetener, and why this capability was maintained for so long and to what purpose.

It is our belief that there is no rational and convincing evidence indicating that there could coexist in primates two distinct types of sweetness receptor, one able to detect in foods the soluble carbohydrates (sucrose, fructose and glucose essentially), the other capable of interacting independently, for rather unclear reasons, with artificial sweet dipeptide(s).

Conversely, and in keeping with the well-known principle of parsimony (see, for example, Milner, 1990), if one accepts the view of the existence of a single type of receptor capable of interacting both with sucrose and sweet dipeptide(s), our results then suggest that the $G_{ALT}$ recognition site could be a necessary requirement for the interaction of sucrose with the sweetness receptor of primates, and that the $G_{APM}$ recognition site could have been a fundamental molecular innovation which appeared in the Old World simian stock, possibly by permitting these primates to improve sensitivity or selectivity to sucrose detection in foods and to facilitate the selection of highly energetic nutriments, especially fruit.

If the above assumption is correct, the appearance of the $G_{APM}$ pocket in the catarrhine sweetness receptor could have been a key factor for the evolution of catarrhine primates by improving food search efficiency and dietary choice for soluble carbohydrates, which could have favoured their mental development, and later the emergence of humans and their evolutionary process (Milton, 1981, 1987).

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